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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/688,794	10/15/2003	Kent Jardemark	58073 (47137)	9727

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EXAMINER	
KOSSON, ROSANNE	

ART UNIT	PAPER NUMBER
1652	

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07/28/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/688,794	JARDEMARK ET AL.	
	Examiner	Art Unit	
	Rosanne Kosson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 November 2009 and 01 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55-62,64,65,67,71,79,81,83,85,87,89-91 and 103-106* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55-62,64,65,67,71,79,81,83,85,87,89-91 and 103-106* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 April 2010* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on November 23, 2009 has been entered. Claim 90 has been amended. Claims 1-54, 63, 66, 68-70, 72-78, 80, 82, 84, 86, 88 and 92-102 have been canceled. Claim 106 has been added. Accordingly, claims 55-62, 64, 65, 67, 71, 79, 81, 83, 85, 87, 89-91 and 103-106 are examined on the merits herewith.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Drawings and Specification

New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because the drawings filed on April 10, 2010 are ambiguous. Applicants are advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

The new drawings are ambiguous, because one reference numeral, "5," for substrate, is used for several different kinds of structures. Each kind of structure should have a different label. In Fig. 3, the substrate (5) is a holder that holds multiple patch clamp electrodes. In Fig. 6, the substrate that looks like the substrate of Fig. 3 is labeled "3," not "5." The "Nanoelectrode

array" should have arrows or brackets referring to the whole device. In Fig. 10A, substrate (5) is a microfluidics channel. In Fig. 10B, substrate (5) appears to be the base and lid of a measurement chamber in which a cell is mounted on a patch clamp electrode. In Fig. 11, substrate (5) is a "Chip substrate" into which a number of parallel grooves have been cut for conducting multiple liquid streams. In Figs. 13 and 14, substrate (5) appears to be a rectangular plate into which a number of converging grooves lined with wells have been cut for conducting multiple liquid streams to a reservoir. As noted above, for clarity, each structure or device should have its own numerical label. For each corrected drawing, the Description of the Drawings should be amended accordingly. Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

Claims 55-62, 64,65, 67, 71, 79, 81, 83, 85, 87, 89-91 and 103-105 remain rejected, and claim 106 is rejected, under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection has been discussed in the previous Office actions.

To reiterate, claims 55 and 60 are confusing and ambiguous in their recitation of the claimed microfluidics system, and the structure of the claimed apparatus still cannot be understood, rendering the meaning of claims unclear. It is not clear if the claimed device is a one-piece structure or a two-piece structure. It is not clear if the substrate is a one-piece device (a molded plate having apertures or tips, an internal or external plumbing system and wells or reservoirs) or a two-piece device (with the apertures and tips in the upper part and the plumbing and wells in the lower part). If the device is a two-piece structure, is the substrate the base (i.e., a modified microtiter plate) or is it the lid for the base? Also, it is not clear what the measurement chamber is. Additionally, the microchannel need not be connected to anything

but the measuring chamber, and the measuring chamber need not be connected to anything. Thus, the structure and how the claimed apparatus is used are unclear.

In claim 55, the substrate comprises a measurement chamber and a raised aperture. The raised aperture comprises a tip, and the tip comprises a housing. But, an aperture is an opening, not a structure. It is not clear if Applicants mean that the measurement chamber comprises some sort of raised structure, raised relative to the substrate, that comprises an aperture, or if Applicants mean something else. It is not clear what the raised structure is. The measurement chamber comprises a microchannel having an inlet somewhere and an outlet that opens into the measurement chamber. But, the relationship of these parts is unclear, particularly the relationship of the aperture, the substrate and the measurement chamber. Further, it is unclear how the microchannel delivers different aqueous streams to the measurement chamber, without the streams mixing together. Claim 60 recites the same apparatus as claim 55 with the change that the aperture is a plurality of solid electrode tips. Applicants have added the functional limitation that the aperture or set of solid electrode tips can detect an electrical property of a lipid material found in cells or of a cell, but this limitation does not serve to add or clarify any structures. Clarification and appropriate correction are again required.

In their Response, Applicants again refer to certain drawings and portions of the specification and assert that these structures are encompassed by the claims. As discussed in the previous Office actions, however, the claims are much broader than the embodiments shown in the drawings. Clear and definite structures must still be recited in the claims. Referring to Fig. 10 B provides an example of one embodiment. But, because the claims have not been amended, they still do not recite any definite structure for the claimed microfluidics system. As for claim 60 and the paragraph referred to on the top of p. 18 of the Response, this

paragraph states that the substrate may have many measurement chambers and that one measurement chamber may have multiple electrodes. This paragraph does not serve to clarify what the structures in claim 60 are or how they are arranged. This paragraph simply states a further aspect of the disclosure. Clarification and appropriate correction are again required.

Claims 90 and 106 are confusing, rendering the meaning of the claims unclear. The previous version of claim 90 had been rejected for being indefinite. Claim 90 recites that the cell or lipid based structure (i.e., cell membrane) is scanned across the microchannel outlet, or the outlet is scanned relative to the cell/membrane, or a fluid is scanned across an immobilized cell/membrane. It cannot be determined what occurs in the "wherein" clauses. Normally, when an object is scanned, a person moves his eyes across it, or a camera or other imaging device moves across it, to make and possibly record an image of the object. Based on Applicants' comments on p. 20 of the Response, however, "scanned" appears to mean "moved." Page 7, first full paragraph of the specification, shows that the word "scanning" has its ordinary meaning. It is not clear how scanning equipment can move cells in the microchannels or how the scanning equipment can move the substrate containing the microchannels relative to the cells. It is not clear how scanning equipment can move streams of fluid across cells. Clarification and appropriate correction are required. In claim 106, the word "scanned" also appears to mean "moved." The fluid stream in the microchannel is moved across an immobilized cell by varying the pressure or the flow rate in the microchannel (increasing the pressure usually increases the flow rate). But, the intended meaning is not clear. A fluid stream cannot be scanned by an imaging device by changing the pressure or the flow rate; the imaging device is moved. Clarification and appropriate correction are required. It is also suggested that Applicants explain how one skilled in the art would know what Applicants meant in these claims at the time of filing.

Claim Rejections - 35 USC § 103

Claims 55-62, 64, 65, 67, 71, 79, 81, 83, 85, 87, 89-91 and 103-105 remain rejected, and claim 106 is rejected under 35 U.S.C. 103(a) as being unpatentable over Maher et al. (US 2002/0025568 A1) and He et al. (US 2003/0049862 A1) in view of Peeters (US 6,123,819) and Hamill et al. ("Improved patch-clamp techniques for high-resolution current recording from cells and cell-free membrane patches," Pflügers Archiv 391:85-100, 1981). This rejection has been discussed in the previous Office actions.

To reiterate, Maher et al. disclose an apparatus for carrying out electrical measurements on cells. The apparatus comprises a substrate comprising an array of measurement chambers (a microtiter plate) that contain cells. The apparatus comprises an array of microelectrodes that match the wells in the microtiter plate and that are arranged in a lid or cover. The electrodes may be solid (i.e., have solid tips) or fluid filled (patch clamp electrodes). Patch clamp electrodes have a tip that is a housing that defines a lumen and that can be inserted into a cell membrane, which is a lipid-based cell structure. The tip has a contacting surface that has a diameter of about one micron, which is a value of less than about one micron, as "about one micron" includes values greater than and less than one micron. The electrode is filled with a conducting electrolyte solution (a buffered salt solution). See Figs. 1, 3 and 9 and paragraphs 11, 15, 127, 136, 137, 143, 144 and 160. See also Hamill et al., p. 86, second full paragraph and right col.; p. 91, left col.; p. 92, left col.; and Figs. 1, 2A, 6A, 9 and 10 on pp. 86, 87, 91, 93 and 94. The apparatus is part of a computer-controlled system that operates the electrical, mechanical and optical aspects of the apparatus, as it controls the activity of the electrodes, movement of the microtiter plate, spectroscopic readings of the wells in the microtiter plate, and data collection and analysis. The electrodes are compatible with microfluidics equipment (see paragraphs 197, 198, 202 and 205-208). Maher et al. do not disclose that the measurement chambers have microchannels.

He et al. disclose a microfluidics system, in which the microfluidics plumbing is incorporated into the lid for a standard microtiter plate, thereby providing the measurement chambers with microchannels. See paragraphs 6-12 and 37-45. The measurement chambers are circular and the microchannels may be radially disposed with outlets in the chambers (see paragraph 39). The system comprises a pressure control device for controlling the positive and negative pressures to the microchannels, which fills and empties the measurement chambers, allowing assays to be performed and the chambers to be washed (see paragraph 49).

The claimed microfluidics system is the apparatus of Maher et al. in which the microtiter plate lid has been modified with the microfluidics plumbing of He et al. It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the microtiter plate of Maher et al. with the microfluidics plumbing for microtiter plate lids of He et al., because He et al. disclose that this modification transforms the apparatus into a high-throughput apparatus, using standard industry equipment, for carrying out the most common types of automated assays used in the biotechnology and pharmaceutical industries, biochemical and genomics assays. Microfluidics chips, by comparison, require specialized custom equipment and have much lower throughput, i.e., they perform far fewer assays in the same amount of time (see paragraphs 6-7) (see claims 55-62, 64, 65, 67 and 103-105).

Regarding claim 71, in modifying the apparatus of Maher et al. with the microfluidics plumbing of He et al., the plumbing (microchannel tubing) would have been inserted in the lid, which is a substrate that is attached to the measurement chambers (see Maher et al., Figs. 1A, 1B and 3). Thus, the substrate comprises measurement chambers. The portion of the microtiter plate that holds the wells is also a substrate. As a result, both the microtiter plate substrate and the lid substrate would have been interfaced to the multi-well plate via the external tubing, because the tubing connects the different portions of the microtiter plate and the

lid via fluid flow (see He et al., paragraphs 43-44 and Figs. 3-4). As a result, this feature does not distinguish the claimed invention over the prior art.

Regarding the computer-controlled equipment for manipulating the microfluidics system (claims 79, 81, 83, 87 and 89-91), as previously discussed, Peeters discloses a microfluidics system comprising a nanoelectrode array on a substrate in a measuring chamber that holds fluids. The array and the chamber are connected to a microfluidics system for the delivery and removal of materials to and from the array via microchannels. The array is connected to a microcontroller or microprocessor, which analyzes signals from the microelectrodes and controls the microfluidics system. The pressure in the microchannels is controlled by an external micro-pump (see Figs. 1-3 and 5; col. 3, lines 21-35; and col. 8, line 38, to col. 9, line 7). Scanning of the nanoelectrode array in the x-y plane at specific positions is computer-controlled and very precise, similar to scanning a DNA chip, and scanning may be performed with a laser. Thus, the laser can scan a cell structure such as protein on the array relative to a microchannel outlet when the chip array of Figs. 1-3 is used in one of the chambers in Fig. 5. Signals from the electrodes can be amplified via transistors. See col. 10, lines 20-30; and col. 10, line 41, to col. 11, line 6). It would have been obvious to one of ordinary skill in the art at the time of the invention to use the computer-controlled equipment of Peeters with the apparatus of Maher et al. (modified with the plumbing of He et al.), because, as noted above, Maher et al. disclose that their apparatus is designed for use with computer-controlled equipment. Peeters discloses the same computer-controlled equipment but is more explicit about the specific tasks and operations that the equipment performs.

Regarding claim 85, as previously discussed, Peeters does not disclose that the operation of the scanning mechanism (e.g., the rate, direction or number of repetitions of scanning) is responsive to a signal from the detector. But, it would have been obvious to one of

ordinary skill in the art at the time of the invention that, if an electrode or a portion of an electrode array, during an experiment, showed one or more regions of interest (e.g., particularly high or low amounts of bound molecules or cell fragments), the software controlling the scanner would have been manipulated to scan in greater detail those regions of interest. Those regions of interest would have been scanned at a different speed to obtain better resolution, and multiple scans would have been performed. Therefore, this claim does not distinguish the claimed invention over the prior art.

Regarding claim 90, as discussed above, it cannot be determined from the claim language where the cell that is scanned is located in one of the microchannels or in the apparatus or what scanning is. Nevertheless, in order to proceed with examination, the claim appears to mean that the imaging information for a cell is retained as the microchannels or the cells in them are scanned. A scanner can scan the cells, but it cannot move them. The laser scanner and the imaging equipment would have been readily programmed by one of ordinary skill in the art at the time of the invention to detect one or more cells at any desired location within a measurement chamber or within a microchannel and to scan the entirety of the measurement chambers and the microchannels (i.e., the entire microtiter plate). Therefore, this claim does not distinguish the claimed invention over the prior art.

Regarding claim 106, similarly, an interpretation is needed to proceed with prosecution. This claim has been interpreted to mean that a fluid stream is scanned as it moves over an immobilized cell. The fluid stream moves over the cell by controlling the pressure and the flow rate in the microchannel. As discussed above, controlling the pressure and flow rate in the microchannels is part of operating a microfluidics system, including the claimed microfluidics system. In scanning the fluid over a cell, the area below the top fluid, including the cell, is also scanned, thereby creating an image of the cell in order to detect changes in the cell (to check

cell health or cell surface reactions). These features, therefore, do not distinguish the claimed invention over the prior art.

Applicants assert that the claimed invention is not obvious, because the device of Maher et al. does not anticipate the claimed invention and has a different structure than that described on p. 56, first full paragraph, of the specification. In reply, as discussed previously and above, the rejection is one of obviousness over the combination of cited references, in particular the device of Maher et al. modified with the plumbing of He et al., for the simplicity and speed of fluid transfer in and out of the measurement chambers. The plumbing of He et al. provides for a high-throughput screening device. The rejection is not one of anticipation over Maher et al. This argument, therefore, does not serve to overcome the rejection.

Applicants assert that the claimed invention is not obvious, because, if one were to combine the teachings of Maher et al. and He et al., one would not arrive at Applicants' invention. In reply, Applicants have not explained this point. Applicants have not explained how one would not arrive at the invention as claimed. Applicants have not linked this argument to any claim limitations. This argument, therefore, does not serve to overcome the rejection.

Applicants assert that the claimed invention is not obvious, because Peeters et al. do not teach patch clamp electrodes; they teach a different type of nanoelectrodes to which cells bind. In reply, it is clear in the previous Office actions that Peeters et al. were not cited for teaching patch clamp electrodes. Patch clamp electrodes are taught by Maher et al. and Hamill et al. It is clear that Peeters et al. were cited for their teachings of a computer-controlled microfluidics system, in which the fluid flow is controlled via computer-controlled fluid pressure regulation and in which a scanner can move anywhere in an x-y plane above the microfluidics device (having a measurement chamber and microchannels). As discussed above, it would have been obvious to use the computer-driven electronics and scanner of Peeters et al. with a microfluidics device

that is the combination of Maher et al. and He et al. for precise control, improved performance and complete imaging capability. This argument, therefore, does not serve to overcome the rejection.

In view of the foregoing, a holding of obviousness is again required.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is (571)272-2923. The examiner can normally be reached on Tues., Wed., Fri., 8:30-6:00, Mon., 8:30-2:00, Thurs. off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Rosanne Kosson
Examiner, Art Unit 1652
2010-07-20

/Karen Cochrane Carlson/
Primary Examiner, Art Unit 1656